REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 112, are respectfully requested in light of the following remarks.

STATUS OF CLAIMS

Claims 1, 3-15, 20, 21, 23, 26, 27, 30-35 and 38-40 are present in this application. Claims 2, 16-19, 22, 24, 25, 28, 29, 36 and 37 were previously cancelled. Claims 1, 4 and 5 have been amended. Claims 39 and 40 have been added.

DISCUSSION OF CLAIM AMENDMENTS

Claim 1 has been amended to more accurately recite the change in the form of the composition from a liquid to a gel, and to recite the hysteresis regarding the gel/liquid and liquid/gel transition temperatures. Support for gel forming after administration is found at least on page 9, line 30 - page 10, line 5 and page 20, lines 26-33 of the specification. Support for the hysteresis is found at least on page 2, lines 34-39, page 10, lines 10-31 and page 11, line 32 - page 12, line 6 of the specification.

Claims 4 and 5 have been amended to recite the gel form has the claimed transition temperature. Support for his amendment is found at least on page 2, lines 34-39, page 10, lines 10-31 and page 11, line 32 - page 12, line 6 of the specification.

Claims 39 and 40 have been added. These claims depend from claims 21 and 33 respectively and recite "the temperature at the site of injection is cooled below the liquid to gel transition temperature." Support for his amendment is found in the specification on page 14, lines 1-8 and in original claim 2.

No new matter has been introduced by these claim amendments.

STATEMENT OF INTERVIEW SUMMARY

Applicants gratefully acknowledge the telephonic interview of June 10, 2009 between Applicant's representative, Gary Mangels, Examiner Sasan and Supervisory Examiner Woodward. Differences between the current invention and the prior art was pointed out with regard to the hysteresis observed in the gel/liquid and liquid/gel transitions Differences between the structures of the organogeling substances of the current invention and the N-acyl amino acid derivatives cited in U.S. Patent No. 5,843,407 were also discussed. Consideration of arguments and/or amendments related to these areas was discussed.

REFERENCE PROVIDED

Applicants have provided a copy of a review article - Organogels and their use in drug delivery - A review, A. Vintiloiu and J. Leroux, Journal of Controlled Release 125 (2008) 179-192. The Examiners attention is directed to section 2.1.2.1. Lecithin organogels, which describes organogels formed from lecithin, a phospholipid. Applicants note that there is no mention, or suggestion, in the review article that organogels formed from lecithin or phospholipids have different gel/liquid and liquid/gel transition temperatures.

CLAIM REJECTIONS - 35 U.S.C. § 103(a)

Claims 1, 3-16, 20, 21, 23, 26, 27 and 29-38 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Fanara et al. (U.S. Patent No. 6,464,987) in view of El-Nokaly et al. (U.S. Patent No. 5,843,407). Applicants submit that this newly made rejection is untenable against the claims now in this application and should be withdrawn.

Applicants respectfully submit that claims 1, 3-16, 20, 21, 23, 26, 27 and 29-40 are not obvious over Fanara and El-Nokaly.

To establish a *prima facie* case of obviousness, three basic criteria must be met. (MPEP 2143) First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Secondly, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The subject matter of Claim 1 of the present application, which is the only independent product claim herein, is a heat-sensitive composition in liquid form, comprising:

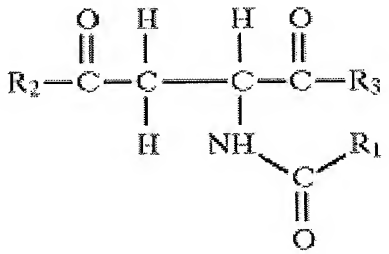
- a hydrophobic organic liquid,
- an organogelling substance which is selected from the group consisting of N-lauroyl-L-alanine methyl ester (LAM), N-lauroyl-L-alanine ethyl ester (LAE), N-stearoyl-L-alanine methyl ester (SAM) and N-stearoyl-L-alanine ethyl ester (SAE), and
- a bioactive substance,

wherein the composition changes from a liquid to a gel form after its administration to an animal body and remains in gel form at the body temperature of said animal body and said gel form has a gel/liquid transition temperature that is higher that the liquid/gel transition temperature.

Fanara et al. disclose fluid pharmaceutical compositions for controlled release of active substance. However, these compositions contain phospholipids as organogelling substances. The specification of the instant invention states at [0036] that lecithins, with are phospholipids, do not constitute gelling substances in the instant invention. Fanara et al. do not teach any organogelling substance which is an amino acid derivative, much less the four specific compounds LAM, LAE, SAM and SAE required in the instant claims. Fanara et al. teaches "these compositions having the property of gelling instantaneously in the presence of an aqueous phase." (col. 3, lines 33-35) Furthermore, Fanara et al. does not teach that the composition

forms a gel that has a gel/liquid transition temperature that is higher than the liquid/gel transition temperature.

El-Nokaly et al. relates to lipstick compositions which comprise a gelling agent selected from the group consisting of hydrophobic silicas, hydrophobic clays with an effective amount of an activator, propylene carbonate, ethyl cellulose, n-acyl amino acid amides and n-acylamino acid esters and mixtures thereof. (col. 5, lines 10-14). The gelling agents include N-acyl amino acid amides and N-acyl amino acid esters as disclosed in PCT Application WO93/03887. (col. 7, lines 41-43) An examination of WO93023008, the published version of PCT Application WO93/03887, discloses various N-acyl amino acid amides and 12-hydroxystearic acid, but does not disclose N-acyl amino acid esters. The N-acyl amino acid derivatives are taught to be prepared from glutamic acid, alanine, lysine, glutamine, aspartic acid and mixtures thereof, (col. 7, lines 41-47). Preferred gelling agents are taught to be n-acyl glutamic acid amides and n-acyl glutamic acid esters of the structure:



(col. 7, lines 45-62). The patent also names a number of specific gelling agents of this type, which are referred to as preferred secondary gellants (col. 7, line 64 to col. 8, line 14). Every specific gelling agent named there is an amide of glutamic acid. The only specific gelling agent of this type exemplified in the patent is N-lauroyl-L-glutamic acid-di-n-butyl amide, which is named as the gelling agent in Examples VII and VIII. Applicants' claims require a gelling agent selected from LAM, LAE, SAM and SAE. El-Nokaly neither discloses nor suggests any specific alanine ester derivatives, much less the four specific alanine esters required by the instant application. El-Nokaly discloses the use of the gelling agent in a lipstick where the gelling agent facilitates the retention of emollient oils. However there is no suggestion to use these gelling agent in a composition that: (1) can be administered within the body; (2) changes from a liquid to a gel after administration within the

body, and (3) forms a gel that has a gel/liquid transition temperature that is higher that the liquid/gel transition temperature.

To establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. There is no suggestion or motivation in Fanara and El-Nokaly to modify these references to obtain the method of the present invention. Fanara teaches the use of a phospholipid as the gelling agent. As shown above, the instant specification states that lecithin, a phospholipid, is not an organogelling agent in the context of the present invention. Fanara does not teach that the gel form has a gel/liquid transition temperature that is higher that the liquid/gel transition temperature, as required by the instant claims. Fanara also does not teach that the composition is "heat-sensitive", which is defined in the specification as being "any composition capable of changing from the liquid state to the gel state as a function of the temperature." (page 1, lines 24-26) (Emphasis added) The Office Action alleges that "this is not persuasive because Fanara teaches compositions that are fluid and that a gel forms under the skin or in the muscle." (page 3, paragraph 4). This overlooks several important teachings in Fanara. Fanara teaches "these compositions have the property of gelling instantly in the presence of an aqueous phase." (col. 1, line 65-67) This teaches that gelling is the result of the aqueous phase, but does not have any teaching regarding temperature. Temperature is mentioned in Fanara with regard to U.S. Pat. No. 5,143,934 which describes compositions which allow the administration, by controlled release, of an active substance in a periodontal pocket, and which comprise at least one monoglyceride and at least one plant oil in proportions which are sufficient to form a liquid crystal phase upon contact with the water present in the periodontal pocket. These compositions are solid at room temperature, but they have a melting point which is lower than body temperature. This teaching is unrelated to the temperature relationship required by the claims of the instant application. The specification of the instant application distinguishes the invention over gels in the prior art, such as those using lecithin, a phospholipid, by stating that the "In contrast [to organogels

containing lecithin] the hydrophobic organogel of the present invention is not formed by absorption of the surrounding water." (page 6, lines 23-25). El-Nokaly teaches lipstick compositions which comprise a gelling agent selected from the group consisting of hydrophobic silicas, hydrophobic clays with an effective amount of an activator, propylene carbonate, ethyl cellulose, n-acyl amino acid amides and n-acylamino acid esters and mixtures thereof. The gelling agents encompassed by the numerous classes of compounds and substances in El-Nokaly involve very large numbers of potential compounds that would need to be evaluated. The Office Action states:

> El-Nokaly teaches n-acyl amino acids esters that are suitable gelling agents and one of ordinary skill in the art would find the specific amino acid derivatives, LAM, LAE, SAM and SAE, obvious variants of the broad group of n-acyl amino acid esters. It would have been obvious to one of ordinary skill in the art at the time the invention was made to choose from a finite number of predictable n-acyl amino acid esters as gelling agents with a reasonable expectation of success of producing a functional product with an organogelling substance. (page 4, second full paragraph)

The use of one of the four specific alanine esters required by the instant claims are not obvious variants because the use of one of these four specific compounds is required for the composition to change from a liquid to a gel form where the gel form has a gel/liquid transition temperature that is higher that the liquid/gel transition temperature. There is nothing in El-Nokaly that teaches or suggests that the use of one of these four specific alanine esters has such an effect on these transition temperatures of the gels. One of ordinary skill in the art, upon reading El-Nokaly would not be motivated to select the four specific alanine esters from the large number of possible gelling agents. El-Nokaly teaches away from using an alanine ester by only mentioning n-acyl amino acid esters as disclosed in PCT Application WO93/03887 while teaching glutamic acid amides and esters having a specific generic structure and numerous specific glutamic acid derivatives. A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out it the reference, or would be led in a direction divergent from the path that was taken by the

applicant." *In re Gurley*, 27 F3d 551, 553, 31 USPQ2d 1130, 1131. (Fed. Cir. 1994) One of ordinary skill in the art upon reading El-Nokaly would not be motivated to select one of four unnamed alanine esters. Because El-Nokaly teaches the gelling agents are used in solid compositions, not compositions that change from a liquid to a gel, one would not be motivated to use the teachings of El-Nokaly. However, assuming such a person was to disregard this aspect of El-Nokaly, such a person would be motivated to explore the use of glutamic acid derivates, which are extensively taught in El-Nokaly. El-Nokaly cannot teach or suggest such the change in the gelling properties of the composition from the use of claimed alanine compounds because it does not teach the composition changing from a liquid to a gel form. Therefore, there is no suggestion or motivation, either in the cited reference itself or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings to obtain the invention of the instant application.

To establish a *prima facie* case of obviousness, there must be a reasonable expectation of success. There cannot be a reasonable expectation of success in obtaining a composition that forms a gel form, where the gel form has a gel/liquid transition temperature that is higher that the liquid/gel transition temperature. There is nothing in Fanara and El-Nokaly that suggests a composition that forms a gel form, where the gel form has a gel/liquid transition temperature that is higher that the liquid/gel transition temperature. There cannot be a reasonable expectation of success in forming a composition that forms a gel form, where the gel form has a gel/liquid transition temperature that is higher that the liquid/gel transition temperature when neither of the references teach or suggest that this required element would occur. As shown above, the Office Action states:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to choose from a finite number of predictable n-acyl amino acid esters as gelling agents with a reasonable expectation of success of producing a functional product with an organogelling substance. (page 4, second full paragraph)

There cannot be a reasonable expectation of success in replacing the phospholipid gelling agent of Fanara with one of the four specific alanine esters required by the instant claims to produce a composition that changes from a liquid form to a gel form having a gel/liquid transition temperature that is higher that the liquid/gel transition temperature. Neither of the cited prior art references teach or suggest that the replacement of phospholipid gelling agent of Fanara with one of the four specific alanine esters required by the instant claims would produce a composition that changes from a liquid form to a gel form having the claimed transition temperature properties. There cannot be a reasonable expectation of success that the substitution of one element in a composition would change a fundamental property of the composition when the fundamental property of the new composition, the composition changing from a liquid form to a gel form having the claimed transition temperature properties, when such a change is not described or suggested in the prior art. The differences between the gels formed in the instant application and the gels formed in the prior art from lecithin and phospholipids can be seen in the attached article by Anada Vintiloiu and Jean-Christopher Leroux. Section 2.1.1 Solid-matrix organogels describes the gels of the instant invention and structures and Section 2.1.2 Fluid-matrix organogels, especially 2.1.2.1 Lecithin organogels, describes gel produced by lecithin and phospholipids, such as those in Fanara. This article describes the physical differences in the structure of the gels formed in the instant invention and the prior art, as well as the differences in how the gel structures are formed. Therefore there would not be a reasonable expectation of success in obtain the Applicants' invention by combining the teachings of Fanara and El-Nokaly.

To establish a *prima facie* case of obviousness, the prior art reference must teach or suggest all the claim limitations. Neither Fanara nor El-Nokaly teach or suggest the four specific gelling agents and that the composition forms a gel where the gel form has a gel/liquid transition temperature that is higher that the liquid/gel transition temperature, as required in the instant application. Therefore Fanara and El-Nokaly do not teach or suggest all the claim limitations.

Applicant respectfully submits claims 1, 3-16, 20, 21, 23, 26, 27 and 29-40 are allowable over Fanara and El-Nokaly and requests that this rejection be withdrawn.

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions related to this response, or the application in general, it would be appreciated if the Examiner would telephone the undersigned attorney at the below-listed telephone number concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: July 1, 2009

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